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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/629,453	07/29/2003	Jack D. Keene	RBN-001DV	5725

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/629,453	KEENE ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21, 23 and 25-29* is/are rejected.

7)☒ Claim(s) *22 and 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/1/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 5/5/05. Claims 30-33 have been cancelled. Claims 1, 23 and 24 have been amended. Claims 1-29 are pending in the application.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection herein and therefore, this action is final.

Information Disclosure Statement

An information disclosure statement filed 4/1/05 has been identified and the documents considered. The corresponding signed and initialed PTO Form 1449 has been mailed with this action. The documents listed as C50 is an International Search Report, which is not considered to be a document under 37 CFR 1.98. Therefore, the International Search Report has been considered but has been crossed off the 1449 so that it will not appear on the face of any patent issuing from the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants claim a genus of RNA-associated proteins that associate with the mRNP complex with a Kd of about 10^{-6} to 10^{-9}. **This rejection is maintained for reasons of record in the office action mailed 11/2/04 and restated below.**

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

However, there is no actual reduction to practice or clear depiction of the claimed invention in detailed drawings. No structures of the claimed invention are disclosed. The structure of a species is disclosed as the specification discloses examples of RNA associated proteins that are well known in the art. The disclosed species are not representative of the genus because without knowing the Kd of its interaction with an mRNP complex, the invention will not operate as intended. Given the diversity of proteins claimed and the inability to determine which of these will also contain the essential element, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of one example in one genus would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph on pages 6-7 of the amendment filed 5/5/05. Applicants argue that the specification has provided adequate written description of the recited genus in paragraph 44. The specification does not comprise numbered paragraphs. However the pre-grant publication, 2004/0096878, teaches that a component is associated with an mRNP complex if it binds to the complex with a Kd of about 10^{-6} to 10^{-9} or a KD of about 10^{-7} to 10^{-7} or a Kd of about 10^{-8} to 10^{-9} in paragraph 44. For purposes of this argument, this paragraph was referenced.

Applicant's arguments filed 5/5/05 have been fully considered but they are not persuasive. The instant invention is drawn to a method of partitioning cellular mRNP complexes using an RNA associated protein that associates with the mRNP complex with a Kd of between about 10^{-6} to 10^{-9} (claim 19), 10^{-7} to 10^{-9} (claim 20) and 10^{-8} to 10^{-9} (claim 21). The instant specification discloses a variety of RNA associated proteins. However, the Kd of association with mRNP complexes by these proteins is unknown. Furthermore, the specification lacks any guidance as to the structural requirements of a protein that would provide the recited function of a Kd of about 10^{-6} to 10^{-9} and thus the specification has failed to describe the proteins such that the nexus of structure and function is apparent. As support, applicants have pointed to the disclosure in paragraph 44. This paragraph simply states that a component associate with an mRNP complex Kd of between about 10^{-6} to 10^{-9} and in a preferred embodiment 10^{-7} to 10^{-9} or 10^{-8} to 10^{-9}. However, this passage does not provide sufficient written description of these proteins. Adequate written description requires more than a mere statement that the sequence is part of the invention and a reference to a potential method for isolating it. In the instant case, a

person of skill in the art would need to determine which proteins have the recited Kd as the skilled artisan cannot envision which of a large genus of proteins have a Kd of about 10^{-6} to 10^{-9}. Given the lack of disclosure as to the structural requirements, the skilled artisan cannot envision the detailed structure of the broad class of or proteins with Kd about 10^{-6} to 10^{-9} regardless of the complexity or simplicity of the method of isolation

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 8, 11-14, 17, 26 and 29 are rejected under 35 USC 102(b) as being anticipated by Allen et al (MCB, 1998, Vol 18, pages 6014-6022; see entire document). **This rejection is maintained for reasons of record in the office action mailed 11/2/04 and restated below.**

Allen et al teach the isolation of mRNP complexes that comprise gRNA and mRNA associated with gBP21, an RNA binding protein (see e.g. page 6017, col 2, paragraph 3). Immunogenetic beads were generated comprising Dynabeads coated with goat anti-mouse IgGs coupled with purified MAbs (see e.g. page 6015, col 2, paragraph 5). Mitochondrial extract was incubated with the MAb specific beads and UV-cross-linking was performed after immunoprecipitation (see e.g. page 6016, col 1, paragraph 5) to partition the RNAs.

Claims 1, 2, 5-8, 12-15, 17, 25 and 26 are rejected under 35 U.S.C. 102(a) as being anticipated by Antic et al (Genes and Development, 1999, Vol 12, page 449-461; see entire document). **This rejection is maintained for reasons of record in the office action mailed 11/2/04 and restated below.**

Antic et al teach immunoprecipitation of mRNP complexes from cell lysates of human teratocarcinoma, hNT2 thus partitioning the mRNPs from the cell lysate (page 458, column 2, paragraph 2). hNT2 can differentiate into neurons (see e.g. page 450, col 2, paragraph) Cell lysates (biological sample) were combined with monoclonal antibody (ligand) such as anti-gene 10 (page 458, column 2, paragraph 2). The immunoprecipitated complex was separated by binding to protein A beads (page 458, column 2, paragraph 2). The Hel-N1 mRNPs complexes were immunoprecipitated by addition of protein A beads to the cell extract, the ligand (anti-g10) was attached to the solid support and lead to the isolation of the RNAs associated with the transfected Hel-N1 which was then identified by RT PCR (page 458, column 2, paragraph 2-4. NF-M was ultimately identified from these complexes.

Claims 1, 2, 8, 12-14, 17, 26 and 27 are rejected under 35 U.S.C. 102(a) as being anticipated by Reim et al (Experimental Cell Research, 1999, Vol 253, pages 573-586; see entire document). **This rejection is maintained for reasons of record in the office action mailed 11/2/04 and restated below.**

Reim et al teach the partitioning of RNA molecules complexed to NonA protein. Kc cell extracts were combined with a plurality of antibodies such as NonA monoclonal antibody Bj6,

S5, X4, P11 as well as ascites fluid and immunoprecipitated with protein A Sepharose (page 574,column 2, paragraph 3 and page 577, col 2, paragraph 2). Bound RNAs were extracted from the immune precipitated complex and prepared for RNA analysis (page 574, column 2 paragraph 4 and 5). RNA analysis was performed by slot blot analysis (page 581, column 2, last full paragraph).

Claims 1-9, 13-17, 23 and 25-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Keene et al. US (5,773,246; see entire document). **This rejection is maintained for reasons of record in the office action mailed 11/2/04 and restated below.**

Keene et al teach immunoprecipitation of mRNP complexes from various tissues in Rat, which include organs, as well as from HeLa extracts, and Medullablastoma cell extracts (see e.g. col 23, line 44-52 and col 27, line 29-35). RNA isolated from Rat tissues was incubated with g10-Hel-N1 fusion protein prebound to protein-A beads using g-10 antibody, the products were purified and sequenced (see e.g. col 24 line 1-14). Extracts were incubated with rabbit anti-Hel N1 antibodies and immunoprecipitated with Staph A Sepharose beads (column 27, line 29-35). Bound RNAs were recovered by ethanol precipitation and a cDNA-subset library was prepared and the sequences determined by sequencing (column 28, line 1-20). Medullablastoma cells are neuralectodermal tumor-derived cells. The specification teaches that for easily degraded RNAs, the RNA can be crosslinked to the mRNP complex (see e.g. col 20, line 37-47). Furthermore, Keene et al teach substitution of antibodies from sera of patients with cancer to immunoprecipitate Hel-N1 (see e.g. col 21, line 26-35).

Claims 1-6, 12-15, 17 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Buckanovich et al (Molecular and Cellular Biology, June 1997, pages 3194-3201; see entire document). **This rejection is maintained for reasons of record in the office action mailed 11/2/04 and restated below.**

Buckanovich et al teach the recognition of RNA targets by the neuronal protein Nova-1. Adult mice brain nuclei were combined with affinity purified rabbit anti-Nova-1 antibodies and protein.A Sepharose (page 3195,column 1, 3rd paragraph). Bound RNAs were extracted from the immune precipitated complex and prepared for RNA analysis (page 3195,column 1, 3rd paragraph). RNA analysis was performed by RT-PCR to assay glycine receptor 2, Nova-1, HuD, HelNI, clathrin, brain specific Na+ channel (page 3195, column 2, last full paragraph).

Claims 1, 2, 8, 10, 18, and 26 are rejected under 35 U.S.C. 102(a) as being anticipated by Takeda et al (J Immun, 1999, Vol 163, pages 6269-6274). **This rejection is maintained for reasons of record in the office action mailed 11/2/04 and restated below.**

Takeda et al teach the isolation of an RNA-associated protein, Pa, and the identification of RNAs associated with it (see e.g. abstract). The mRNP complex was immunoprecipitated from HeLa cells using antibodies preincubated to protein A sepharose beads isolated from the sera of patients with autoimmune disorders (see e.g. page 6269, col 2, paragraphs 3-4).

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 102 on pages 7-10 of the amendment filed 5/5/05. Applicants argue that none of the references anticipate the instantly

recited claims because they do not teach collecting an mRNP complex by removing it from the solid support.

Applicants' arguments filed 5/5/05 have been fully considered but they are not persuasive. First, applicants appear to be arguing that the step of "collecting the mRNP complexes by removing the mRNP complex from the solid support" distinguishes the instant method from published methods. However, the step of removing immunoprecipitated complexes from solid supports is well known in the art. For example, Korman et al (1982) teach a complex of RNA with protein-A-sepharose-antigen. RNA was isolated from the column by passing it over an oligo(dT)-cellulose column. Finally, the RNA was isolated from the second column by elution in water. Therefore, the removal of biological materials from solid supports for further manipulations is well established in the art.

Secondly, in order to perform subsequent manipulation of any of the components of the mRNP complexes partitioned from a sample i.e. to identify precipitated proteins or RNAs by Western or Northern blot analysis or PCR, the complexes must be removed from the support. If the beads were attached, subsequent analysis would be hindered such as an alteration in migration in a gel. Hence the prior art that teaches subsequent analysis of the proteins or RNA molecules must inherently remove the complexes from the support. For example, Allen et al teach immunoprecipitation of mitochondrial proteins using Mab-specific immunomagnetic beads. Following immunoprecipitation, Allen et al teach that the beads are washed and then incubated with elution buffer (see e.g. page 6015, col 2, paragraph 5). Allen et al by elution, collect and remove the mRNP complex from the solid support as demonstrated by subsequent analysis of the immunoprecipitated gRNAs and mRNAs on a gel (see e.g. page 6019, col 1,

paragraph 2 and figure 5). The RNA bands show no evidence of sepharose A beads. Takeda et al teach also teach that following immunoprecipitation of sera with protein sepharose A, the immunoprecipitate was washed three times and then the proteins were eluted from the beads using SDS-sample buffer (see e.g. page 6270, col 1, paragraph 1). As well, following immunoprecipitation, the beads were washed in NET-2 buffer three times and the nucleic acids extracted and electroporated (see e.g. page 6270, col 1, paragraph 3). Buckanovich et al, Reim et al and Keene et al teach that following co-precipitation of the RNA binding proteins with RNA using protein A sepharose coupled to binding molecules, the RNA is pelleted and analyzed. In each of these cases, analysis of the RNA or protein could not have occurred without removal of the complex from the solid support. Absent evidence to the contrary, in each of the recited methods, the mRNP complex was collected by removing the complex from the solid support as described above for each case individually and therefore, the methods of the instant invention are anticipated.

Thirdly, to the end of "collecting the mRNP complexes by removing the mRNP complex from the solid support", the specification teaches that the mRNP complex is removed from the solid support such as by washing the complex from the support using suitable solvents (page 13, line 17-19). Specifically, in example 1, the specification teaches the P19 cells were transfected with a construct expressing G10tagged HuB. Lysates prepared from the cells were incubated with Protein A sepharose beads to immunoprecipitate the mRNP complexes. Following this, the Protein A sepharose beads were washed 4 times with NT2 buffer and then two times with NT2 buffer supplemented with 1M urea. The washed beads were resuspended in NT2 buffer with SDS and proteinase K and incubated in a 55°C water bath. Following proteinase K digestion, the

RNAs were isolated. The teachings of the specification are not distinct from Antic et al. Antic et al teach immunoprecipitation of mRNP complexes in which the bead-mRNP complex is washed in B4 buffer comprising NP-40 and treated with DNase I and proteinase K. Following digestion, the RNA was extracted and analyzed.

Conclusion

Claims 1-21, 23 and 25-29 are rejected.

Claim 22 and 24 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 571-=273-8300 for regular communications and (703) 872-9306 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Zeta Adams, whose telephone number is (703) 308-01963291.

Maria B Marvich, PhD
Examiner
Art Unit 1633

July 15, 2005

JAMES KETTER
PRIMARY EXAMINER